World Health Organization

Critical review report:

Butonitazene

Expert Committee on Drug Dependence

Forty-sixth Meeting

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This report contains the views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization

Contents

Executive summary

Butonitazene (IUPAC name: 2-(2-(4-butoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)-*N*,*N*-diethylethan-1-amine), also known, for example, as butoxynitazene, is a benzimidazole-derived synthetic opioid with a chemical structure and pharmacological action similar to those of drugs under Schedule I (under the 1961 United Nations Conventions), such as etonitazene and isotonitazene. It is included in a series of 2-benzylbenzimidazole derivatives with analgesic properties that were originally synthesized in the late 1950s; however, no medical use of butonitazene was identified. Butonitazene has not been reviewed previously by the WHO Expert Committee on Drug Dependence.

Butonitazene, usually of unknown purity or concentration, has been detected in seized material. Butonitazene sold as a reference material has been described as a crystalline solid.

No information on the main route used for its administration was found, but a report of analysis of a test sample indicated that butonitazene was smoked.

In-vitro pharmacological studies show that butonitazene is an opioid agonist, with a binding affinity similar to that of mu-opioids such as morphine but lower than that of fentanyl. Butonitazene was less potent than morphine and fentanyl in inducing analgesic effects in the warm-water tail-flick assay.

The presence of butonitazene was confirmed in one post-mortem case, in which the cause of death was attributed to an overdose of metonitazene. Information on the adverse effects of butonitazene from an unverified website indicate typical opioid effects, such as analgesia, euphoria and sleepiness, as well as vomiting and respiratory depression. To date, butonitazene has been identified in eight countries.

No studies have been conducted of its dependence potential in experimental animals or humans. In drug discrimination studies (two-lever choice method) in rats, butonitazene fully substituted for morphine for discriminative stimulus effects, suggesting abuse potential. No studies on the abuse potential of butonitazene in humans were found. It has structural similarities to other Schedule I (under the 1961 United Nations Conventions) synthetic mu-opioid receptor agonists (e.g. etonitazene, isotonitazene).

There are no known therapeutic or industrial uses of butonitazene, and there has been no marketing authorization. It is used as a reference material in scientific research and forensic applications.

Reports from the US National Forensic Laboratory Information System indicate that butonitazene was first detected in Ohio in 2021. A total of 51 occurrences were reported between 2021 and 2022.

Butonitazene is not currently controlled under the 1961, 1971 or 1988 United Nations Conventions.

1 Substance identification

A International Nonproprietary Name

B Chemical Abstracts Service (CAS) Registry Number

95810-54-1 (free base)

118951-34-1 (hydrochloride salt)

Free base

Canonical SMILES

O=N(=O)C=1C=CC2=C(N=C(N2CCN(CC)CC)CC3=CC=C(OCCCC)C=C3)C1

InChI

InChI=1S/C24H32N4O3/c1-4-7-16-31-21-11-8-19(9-12-21)17-24-25-22-18-20(28(29)30)10-13-23(22)27(24)15-14-26(5-2)6-3/h8-13,18H,4-7,14-17H2,1-3H3

InChI key

UZZPOLCDCVWLAZ-UHFFFAOYSA-N

Hydrochloride salt

Canonical SMILES

Cl.O=N(=O)C=1C=CC2=C(N=C(N2CCN(CC)CC)CC3=CC=C(OCCCC)C=C3)C1

InChI

InChI=1S/C24H32N4O3.ClH/c1-4-7-16-31-21-11-8-19(9-12-21)17-24-25-22-18-20(28(29)30)10-13-23(22)27(24)15-14-26(5-2)6-3;/h8-13,18H,4-7,14-17H2,1-3H3;1H

InChI key

WIJPAKBZQWABKM-UHFFFAOYSA-N

C Other chemical names

2-[(4-Butoxyphenyl)methyl]-*N*,*N*-diethyl-5-nitro-1*H*-benzimidazole-1-ethanamine (ACI)

Benzimidazole, 2-(*p*-butoxybenzyl)-1-[2-(diethylamino)ethyl]-5-nitro-(7CI)

1*H*-Benzimidazole-1-ethanamine, 2-((4-butoxyphenyl)methyl)-*N*,*N*-diethyl-5-nitro-

2-[2-[(4-Butoxyphenyl)methyl]-5-nitrobenzimidazol-1-yl]-*N*,*N*-diethylethanamine

2-(2-(4-Butoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)-*N*,*N*-diethylethan-1-amine

Butoxynitazene

D Trade names

Butonitazene is sold as hydrochloride salt under its own name, butonitazene (hydrochloride), as an analytical reference standard *(1)*.

E Street names

Butonitazene is known under its own name or as butoxynitazene *(2)*.

F Physical appearance

A pure analytical standard of butonitazene hydrochloride was described as a crystalline solid *(1)*. Several companies that sell butonitazene on the Internet show the compound as a white or yellow-brown powder (e.g. *3,4*).

G WHO review history

Butonitazene has not been formally reviewed by WHO and is not currently under international control.

2 Chemistry

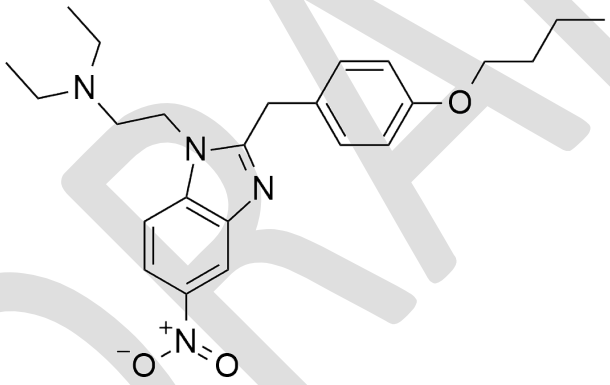
A Chemical name

IUPAC Name: *N*,*N*-Diethyl-2-[(4-butoxyphenyl)methyl]- 5-nitro-1*H*-benzimidazole-1-ethanamine

CA index name
1*H*-Benzimidazole-1-ethanamine, 2-[(4-butoxyphenyl)methyl]-*N*,*N*-diethyl-5-nitro- (ACI)

B Chemical structure

Free base:



Molecular formula: $C_{24}H_{32}N_4O_3$
Molecular weight: 424.54 g/mol

C Stereoisomers

There are no stereoisomers of butonitazene.

D Methods and ease of illicit manufacture

Butonitazene is a 5-nitro-2-benzylbenzimidazole belonging to the series of 2-benzylbenzimidazole compounds developed in the late 1950s as opioid analgesics *(5)*. It is a metonitazene, etonitazene and protonitazene homologue in which the C4 position of the benzyl moiety is substituted by a methoxy, ethoxy and *n*-propoxy group, respectively. The molecule of butonitazene presents an *n*-butoxy substituent on the benzyl moiety.

Synthesis of butonitazene was reported by Hunger et al. *(6)* and more recently by Vandeputte et al. *(7)*. The activated chlorine atom of 1-chloro-2,4-dinitrobenzene can easily be. substituted with 2-diethylaminoethylamine. Subsequently, the nitro group in the *ortho* position can be selectively reduced to yield the corresponding amino function of the *ortho*-phenylenediamine species. The latter can be condensed with *n*-butoxyphenyl imidate, which is obtained from the *n*-butoxyphenylacetonitrile derivative. The reaction affords the 5-nitro-substituted product butonitazene.

Butonitazene can be obtained through other routes for the synthesis of its 5-nitro-2-benzylbenzimidazole homologues (metonitazene, etonitazene and protonitazene) *(8–11)*.

Although no information was found on the actual method and scale of manufacture of butonitazene, the synthetic methods are simple and cost-efficient and do not require regulated precursors *(5)*.

E Chemical properties

Melting-point
Butonitazene hydrochloride: 154–156 °C *(6)*

Boiling-point
No information was found.

Solubility

Butonitazene hydrochloride salt is soluble in dimethylformamide (DMF) at 25 mg/mL and in dimethyl sulfoxide at 20 mg/mL. It was soluble at 0.5 mg/mL in a 1:1 mixture of DMF and phosphate-buffered saline (pH 7.2) and at 10 mg/mL in ethanol *(1)*. No definitive data on the solubility of butonitazene free base or its hydrochloride salt were found.

F Identification and analysis

Synthetic butonitazene has been characterized by Fourier-transform infrared, nuclear magnetic resonance spectroscopy, high-performance liquid chromatography (HPLC) coupled to diode-array detection, gas chromatography coupled to mass spectrometry (MS) and LC coupled to HPLC *(7,12,13)*.

Butonitazene hydrochloride is available as a reference material from commercial suppliers for routine analysis in forensic and clinical investigations *(1)*.

Two LC-MS/MS methods have been published for the identification of butonitazene in human blood in two cases of intoxication *(14)* and in post-mortem blood, serum and urine samples *(15)*.

3 Ease of conversion into controlled substances

It is not known whether butonitazene can be converted into a controlled substance.

4 General pharmacology

A Routes of administration and dosage

One report from the Welsh Emerging Drugs and Identification of Novel Substances Project *(16)* included results from testing of a sample that was smoked. No reports from participants in online discussion forums were found for determining the preferred route of administration or dosage.

B Pharmacokinetics

No data on the absorption, distribution, metabolism or excretion of butonitazene were found. Although the metabolism of butonitazene has not been studied, benzimidazole opioids (which include butonitazene) usually undergo *N*-dealkylation at the *N*-ethylamine chain and *O*-dealkylation at the phenylalkyl chain. It is therefore reasonable to expect that 4´-OH-nitazene might be a major butonitazene metabolite formed through *O*-dealkylation. 4´-OH-Nitazene was detected in serum and quantified in urine at 9.8 ng/mL (although the validation methods were not described) *(17)*.

C Pharmacodynamics

Studies of the binding and functional activity of butonitazene at human delta- and kappa- opioid receptors, and rat mu-opioid receptors transfected into Chinese hamster ovary cells *(18)* showed that the binding affinity of butonitazene is similar to that of mu-opioids such as morphine but lower than that of fentanyl. The binding affinities of butonitazene to delta- and kappa-opioid receptors were lower than those of fentanyl and morphine.

Butonitazene was more potent at mu-opioid receptors than at delta- and kappa-opioid receptors. The agonism of butonitazene to mu-opioid receptors was similar to that of fentanyl and morphine. Further details of the binding and agonism of butonitazene at opioid receptors are presented in Annex 3.

Butonitazene was tested for its ability to produce analgesic effects in the warm-water tail-flick assay in 10 Swiss-Webster mice treated by cumulative dosing (from 0.1 to 10 mg/kg) followed by a time-course of the peak effect of butonitazene. Butonitazene increased tail-flick latency to a maximum of 100% after administration of 10 mg/kg in a dose-dependent manner. Potency ratios (ED_{50} test compound/ED_{50} reference compound) indicated that butonitazene was less potent than morphine and fentanyl. Butonitazene was considered to be as efficacious as morphine and fentanyl. The peak analgesic effects of butonitazene lasted 90 min and returned to baseline after 180 min.

Subcutaneous injection of naltrexone before administration of 3.2 mg/kg butonitazene (peak dose that did not produce adverse effects) blocked the analgesic effect of butonitazene, indicating the involvement of opioid receptors in the action of butonitazene *(19)*. Of note, three mice died, at 45 min, 60 min and 5 min after administration of 10 mg/kg butonitazene. Further details of the analgesic effects of butonitazene are presented in Annex 3.

5 Toxicology

According to the United Nations Office on Drugs and Crime Early Warning Advisory, butonitazene was reported in eight countries between 2019 and 2022 *(20)*; however, no reports were found on the toxic doses of butonitazene for humans.

Butonitazene was reported in one death (a 42-year-old male in Ohio, USA), in combination with metonitazene. The cause of death was attributed to metonitazene overdose. The concentrations of butonitazene were 3.2 ng/mL in peripheral blood (median concentration), 2.4 ng/mL in serum and 10 ng/mL in urine *(15,17)*.

6 Adverse reactions in humans

No reports were found on adverse reactions of butonitazene in humans. Unverified information found online *(21)* referred to analgesia, euphoria, sleepiness, as well as vomiting and respiratory depression at high doses (not specified) of butonitazene.

Butonitazene was analytically confirmed in one death, but the cause of death was attributed to an overdose of another opioid, metonitazene *(17)*.

Activation of the mu-opioid receptor by butonitazene involves interaction with β-arrestin-2 *(22)*. The interaction of β-arrestin-2 with mu-opioid receptors has been shown to mediate some of the adverse health effects of certain opioid analgesics. For example, morphine has been shown to cause less physical dependence, constipation and respiratory suppression in β-arrestin-2 knockout mice than in wild-type mice *(23)*.

7 Dependence potential

A Studies in experimental animals

No studies were identified.

B Studies in humans

No studies were identified.

8 Abuse potential

A Studies in experimental animals

In drug discrimination studies (two-lever choice method), butonitazene fully substituted for the discriminative stimulus effects of 3.2 mg/kg morphine after subcutaneous administration to eight Sprague-Dawley rats at a dose of 0.1–3.2 mg/kg. Assessment of the potency ratio (ED_{50} test compound:ED_{50} reference compound) showed that butonitazene was more potent than morphine but less potent than fentanyl. Butonitazene was considered to be as efficacious as morphine and fentanyl. Subcutaneous injection of naltrexone to rats before administration of 3.2 mg/kg butonitazene blocked the morphine-like discriminative stimulus effects of butonitazene, indicating the involvement of opioid receptors in the discriminative stimulus effects of butonitazene *(24)*. Details of the discriminative stimulus effects of butonitazene are presented in Annex 3.

B Studies in humans

No studies of the abuse potential of butonitazene in humans were identified.

9 Therapeutic applications and extent of therapeutic use and epidemiology of medical use

Synthesis of a group of benzimidazole derivatives with analgesic properties was described in 1957 *(25)*; however, none of the derivatives were medically approved.

Butonitazene is not known to have any medical use.

10 Listing on the WHO Model List of Essential Medicines

Butonitazene is not listed on the 23rd WHO List of Essential Medicines or the 8th WHO List of Essential Medicines for Children.

11 Marketing authorizations (as a medicinal product)

Butonitazene is not known to be authorized for marketing.

12 Industrial use

Butonitazene is not known to have any industrial use.

13 Non-medical use, abuse and dependence

No information was found on nonmedical use or dependence on butonitazene.

Butonitazene was identified on an online forum (*16)*, in a sample received by a purchaser who had intended to buy 5-CLA-DBA, suggesting unintentional use. Butonitazene was detected in 51 reports from the US National Forensic Laboratory Information System between 2021 and 2022 *(26)*, as further described in section 16.

14 Nature and magnitude of public health problems related to misuse, abuse and dependence

No information was found on the nature or magnitude of health problems associated with butonitazene.

15 Licit production, consumption and international trade

Butonitazene is used as reference material in scientific research and forensic applications.

16 Illicit manufacture and traffic and related information

Reports from the US National Forensic Laboratory Information System indicate that butonitazene was first detected in the USA in January 2021, in Ohio. Between 2021 and 2022, butonitazene was mentoined in 51 reports in the following US states: Alabama (1), Florida (4), Iowa (1), Kentucky (3), Ohio (34) and West Virginia (8). Of the 39 reports in 2021, 26 included weights, totalling 824.48 g *(26)*.

According to the United Nations Office on Drugs and Crime Early Warning Advisory on New Psychoactive Substances (2022), butonitazene was reported in eight countries between 2019 and 2022 *(20)*.

17 Current international controls and their impact

Butonitazene is not currently controlled under the 1961, 1971 or 1988 United Nations Conventions.

18 Current and past national controls

Butonitazene is a Schedule I controlled substance in the USA.

Butonitazene is controlled as Class B by the United Kingdom Misuse of Drugs Act.

In Germany, butonitazene is classified as "Neue-psychoaktive-Stoffe-Gesetz", which authorizes its use only for industrial and scientific purposes.

19 Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

No other matters were identified.

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